

## Research article

# Morphological types of breast cancer in family members and multiple primary tumours: is morphology genetically determined?

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## Abstract

**Background:** We conducted the present study to determine whether breast cancer morphology is genetically determined.**Methods:** Using the nationwide Swedish Family Cancer Database, which includes data on 10.2 million individuals and over 25,000 morphology-specific breast cancers, we followed morphological types in familial cancers between mothers and daughters and between sisters. Additionally, we recorded morphological data in women who presented with two primary breast cancers and in those who presented with an invasive and *in situ* breast cancer. We used kappa statistics to examine the association between genetics and morphology. A kappa value of 0 indicates that the process is random and a value of 1 indicates that it is completely determined (i.e. genetic); values between 0.40 and 0.60 are considered to indicate a moderately determined process.**Results:** The study sample included a total of 25,730 first and 3394 second invasive breast cancers, and 2990 *in situ* breast cancers. Ductal, lobular, tubuloductal and comedo were the most common invasive types. We identified 164 mother–daughter pairs with breast cancer of a defined morphology, yielding a low kappa value of 0.08. Among 100 sister pairs the kappa value was 0.002. In individuals with two primary breast cancers the kappa values were 0.22 and 0.01 for two invasive and *in situ*–invasive pairs, respectively. However, for a tumour with a subsequent tumour detected in the contralateral breast less than 1 year later the kappa value was 0.47.**Conclusion:** The data suggest that breast cancer morphology is not genetically determined. However, because of mixed morphologies and the overwhelming prevalence of ductal morphology, the results for rare morphologies should be interpreted with caution.**Keywords:** ductal cancer, familial cancer, genetic effect, lobular cancer, second primary

## Introduction

Tumours of the breast are believed to arise from terminal ductal lobular units and comprise two common morphological types: ductal and lobular neoplasia [1]. Rarer morphological types include tubuloductal, comedo, medullary, mucinous and Paget types [2]. Morphological type has implications for treatment and prognosis, and it

would be of interest to determine whether morphological type is genetically determined.

Breast tumours often present with mixed morphological types, suggesting that in such cases a single genetic background can give rise to tumours of multiple morphologies. It is also known that lobular *in situ* cancers may give

rise to ductal invasive cancers [2,3]. Very limited data are available on morphological types in familial and heritable breast cancer. The only consistent morphological features in breast cancers associated with mutations in the *BRCA1* and *BRCA2* genes are the lower frequencies of lobular morphology as compared with the frequencies in *BRCA1/2*-unrelated familial breast cancers [4,5]. *BRCA1*-related tumours exhibit a small excess of medullary-like morphology. *BRCA1/2*-related breast cancers also tend to have ductal or lobular *in situ* histology less frequently than do all breast cancers combined [5]. Familial breast cancers that are unrelated to *BRCA1/2* have not shown any significant morphological difference from all breast cancers combined [4]. On the basis of earlier small studies, it was assumed that mutations in the E-cadherin gene are only present in lobular breast cancer; this was not confirmed in a recent larger study, however, which identified mutations in the E-cadherin gene in ductal cancer also [6].

In the present study we used the nationwide Swedish Family Cancer Database to examine the morphological types of breast cancer in family members and in individuals with two primary tumours [7]. The Database was updated in 2001 to include over 10 million individuals and over 1 million registered tumours, retrieved from the Swedish Cancer Registry for the years 1958–1998. It offers unique possibilities for reliable estimation of familial risk because the data on familial relations and cancers were obtained from registered sources with practically complete coverage. The Swedish Cancer Registry has used the International Classification of Diseases (ICD) coding system ICD-O-2 since 1993. Thus, the specific morphological classification covers only 6 years, but because of its nationwide coverage a large number of breast cancer patients are included.

We conducted the present study in order to determine whether morphological type defines a discrete genetic background.

## Patients and methods

The Swedish Family Cancer Database was initially created during the mid 1990s by linking an administrative family register on all Swedish families to the Swedish Cancer Registry [7–9]. For each child there are data on both parents at the time of birth. Each person has been assigned a unique identification number (which is different from the national identification number – the ‘personal number’); this allows construction of families, for example, through the mother. The Database includes data for all persons born in Sweden after 1931, along with data for their biological parents, totalling over 10.2 million individuals. It was updated at the start of the year 2001 to include cancers from the nationwide Swedish Cancer Registry for the years 1958–1998. The Database is organized into 3.2 million families (parents and offspring).

The completeness of cancer registration during the 1970s has been estimated at over 95%, and is now considered to be close to 100%. The percentage of cytologically or histologically verified breast cancer cases is close to 100% [10]. The Swedish Family Cancer Database has incomplete linkage from deceased offspring to parents, particularly among those born between 1932 and 1940. Out of a total of 7.0 million offspring, 216,000 had died by the end of follow up (31 December 1998). Parental information was missing for 15,000 deceased offspring who had a diagnosis of cancer (9.9% of all cancers in offspring). This deficit is unlikely to have any significant impact on the findings of the present study.

The Swedish Cancer Registry is based on compulsory notification of cases [10]. A four-digit diagnostic code, in accordance with the 7th revision of the ICD, was used until the year 1992; thereafter, the ICD-O-2 coding system was employed. In cases of multiple morphological types, the notifications considered the most common morphology. Among first and second breast cancers, and *in situ* and invasive cancers, all cases were included; however, the analysis considered whether second cancers occurred in the same breast or in the contralateral one, and the time interval between diagnoses.

Family history information was collected for all first-degree relatives (parents, siblings and children), but only mother–daughter and sister–sister relationships were considered in the present study. In a small number of families three or more sisters were affected, but they were not included in the present analysis.

Statistical analysis was based on kappa statistics as a measure of agreement between morphologies; kappa values are calculated using the following equation [11,12].

$$\text{Kappa} = \frac{\text{observed number of cases} - \text{expected number of cases}}{1 - \text{expected number of cases}} \quad (1)$$

Kappa can take values between –1 and 1; 0 indicates complete chance occurrence, and –1 or 1 indicates a process that is completely determined. Values between 0.40 and 0.60 are considered moderately determined. For simplicity, in the present report we present only positive values of kappa by deleting the minus sign. The kappa values are unweighted, but all findings were also tested using the weighted kappa test, with unaltered results [11]. Some tests were also done on selected morphological types.

Use of the Swedish Family Cancer Database was approved by the Ethics Committee of the Karolinska Institute, south.

**Table 1****Number of morphology-specific breast cancers in the Swedish Family Cancer Database during the period 1993–1998**

Morphology	1st invasive		2nd invasive		<i>In situ</i>	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Ductal	14,187	66.2	1679	60.9	1834	69.9
Lobular	2936	13.7	531	19.2	324	12.4
Tubuloductal/tubular	1915	8.9	232	8.4	2	0.1
Comedo	1190	5.6	133	4.8	397	15.1
Mucinous	608	2.8	87	3.2	0	0.0
Medullary	340	1.6	29	1.1	0	0.0
Papillary	117	0.5	24	0.9	55	2.1
Morbus Paget	100	0.5	43	1.6	11	0.4
Cystosarcoma phyllodes	47	0.2	1	0.0	0	0.0
Other	4290		635		367	
All	25,730		3394		2990	

Percentages are for all cancers apart from those in the 'Other' category (undefined morphological types). Thus, for first primary the percentages provided are from a total of 21,440 cancers, for second primary they are from a total of 2759 cancers, and for *in situ* they are from a total of 2623 cancers.

## Results

The Swedish Family Cancer Database covers the years 1958–1998 from the Swedish Cancer Registry, but because specific morphology has been recorded since 1993 we included only those breast cancers that were diagnosed between 1993 and 1998. Familial breast cancer was defined as those cases in which breast cancer was diagnosed in a mother or sister of the index patient during the period from 1993 to 1998.

The numbers of morphology-specific breast cancers are shown in Table 1. A total of 25,730 first and 3394 second invasive breast cancers, and 2990 *in situ* breast cancers were recorded during the 6-year period from 1993 to 1998 in Sweden. Ductal and lobular invasive, and *in situ* cancers were the most common forms; the group 'other' mainly included undefined morphological types, termed 'adenocarcinoma'. For *in situ* cancers some morphologies, such as tubuloductal, mucinous, medullary and cystosarcoma phyllodes, were not used. The comedo type was relatively more frequent among *in situ* (15.1%) than among invasive cases (5.6%).

Table 2 shows the distribution of morphology-specific breast cancers between mothers and daughters, diagnosed during the years 1993–1998. Only the three most common morphological types are shown separately. A total of 164 mother–daughter pairs were analyzed and a kappa value of 0.08 was calculated, indicating that the morphologies of familial cancers between two generations were entirely random. A similar analysis was carried out

**Table 2****Numbers of familial breast cancers in mother and daughter by morphology**

Daughter	Mother				
	Ductal	Lobular	Tubuloductal	Other	All
Ductal	52	8	6	36	102
Lobular	8	2	0	7	17
Tubuloductal	11	0	1	1	13
Other	20	4	2	6	32
All	91	14	9	50	164

Kappa value for all types 0.08.

between sisters, amounting to 100 pairs (Table 3). The kappa value was 0.002, indicating that the morphology between sisters was also entirely random.

Multiple primary breast cancers were also considered (Table 4). In 907 women, two primary cancers were diagnosed. The overall kappa value was still low, at 0.22, but there were some types that appeared to be less random. Among 147 women with first lobular cancers, 55 presented with a second lobular cancer. However, the kappa value was almost equal, at 0.23, when only ductal and lobular morphologies were tested. Similarly, among 66 tubuloductal first cancers, 14 women were subsequently diagnosed as having a second tubuloductal cancer. The relationships between *in situ* and invasive breast cancer

**Table 3****Numbers of familial breast cancers in sisters by morphology**

Sister 1	Sister 2				All
	Ductal	Lobular	Tubuloductal	Other	
Ductal	39	8	4	7	58
Lobular	6	2	1	4	13
Tubuloductal	11	1	0	1	13
Other	10	3	1	2	16
All	66	14	6	14	100

Kappa value for all types 0.002.

among 465 women are shown in Table 5. The overall kappa value was low, at 0.01, but some combinations of *in situ* and invasive cancers (i.e. comedo with ductal, and lobular with tubuloductal) appeared commonly.

In Tables 4 and 5 all first and second cancers are considered irrespective of laterality or timing between the two. These variables influenced kappa values (Table 6). For the first/second invasive cancer sequence, kappa values increased when the second cancer was diagnosed in the contralateral breast (from 0.22 to 0.38) and marginally when it was diagnosed less than 1 year from identification of the first cancer (0.23). When both of these conditions were met, the kappa value was 0.47, indicating moderate dependence between the morphologies. With these conditions, the kappa value was 0.63 when only ductal and lobular types were tested. The reason for these increased kappa values was that lobular tumour was often followed

by another lobular tumour. Kappa was 0.40 even when ductal and lobular types were tested separately for contralateral breast cancers diagnosed more than 1 year apart. Similarly, in the *in situ*/invasive sequence, the kappa value was 0.33 when contralateral breasts were affected within 1 year. All of the kappa values were lower in the *in situ*/invasive sequence than in the first/second breast cancer sequence.

## Discussion

We used the kappa test in the present analysis to test whether the morphologies of two breast cancers in family members or within the same individuals were of similar or different types [11,12]. A word of caution is in order here because the test considers the numbers of events, and common types of events are weighted more than are rare events. The ductal type, being the dominant morphology, may overshadow the patterns of rare types. Moreover, breast cancer is often of mixed morphology at presentation [3], and only the main type was recorded in the Swedish Cancer Registry. The problem of dominance can be avoided by testing individual rare types separately, but for small numbers of cases the random variation may be large. Thus, the familial cancers were so few in the present study that it was not meaningful to test separately the patterns for rare morphologies.

The data used in the present analysis were taken from the Swedish Family Cancer Database, which has almost complete nationwide coverage of families and cancer cases [7–9]. Although morphological classification has been used for only 6 years (from 1993 to 1998), the database includes information on over 25,000 first invasive and almost 3000 *in situ* cases.

**Table 4****Numbers of breast cancers in women with first and second invasive breast cancer by morphology**

1st invasive	2nd invasive									All
	Ductal	Lobular	Tubuloductal	Comedo	Medullary	Mucinous	Mb Paget	Papillary	Other	
Ductal	224	77	36	14	3	8	18	2	51	433
Lobular	56	55	23	3	0	0	1	0	9	147
Tubuloductal	25	17	14	2	0	2	0	1	5	66
Comedo	13	5	3	12	0	1	8	0	7	49
Medullary	4	1	0	5	0	1	0	0	1	12
Mucinous	11	3	4	0	0	5	0	0	2	25
Morbus Paget	5	2	0	1	1	0	0	0	1	10
Papillary	3	0	2	0	0	1	0	0	0	6
Other	51	12	9	1	0	2	0	0	84	159
All	392	172	91	38	4	20	27	3	160	907

Kappa value for all types 0.22; kappa value for ductal and lobular 0.23; kappa value for ductal, lobular and tubuloductal 0.18.

**Table 5****Numbers of breast cancers in women with invasive and *in situ* breast cancer by morphology**

<i>In situ</i>	Invasive									All
	Ductal	Lobular	Tubuloductal	Comedo	Medullary	Mucinous	Morbus Paget	Papillary	Other	
Ductal	77	37	44	7	2	15	9	3	13	207
Lobular	63	12	37	12	1	1	2	0	6	134
Tubular	0	0	0	0	0	0	0	0	1	1
Comedo	45	7	11	4	1	4	5	0	2	79
Morbus Paget	2	0	0	1	0	0	0	0	0	3
Papillary	4	1	2	0	0	0	0	0	0	7
Other	13	1	2	1	0	0	0	0	17	34
All	204	58	96	25	4	20	16	3	39	465

Kappa value for all types 0.01; kappa value for ductal and lobular 0.18; kappa value for ductal, lobular and tubuloductal 0.08.

**Table 6****Kappa measures of agreement**

		Kappa		
Condition	<i>n</i>	All types	Ductal and lobular	Ductal, lobular and tubuloductal
1st/2nd invasive				
Include all	907	0.22	0.23	0.18
Contralateral breast	653	0.38	0.56	0.47
<1 year interval	643	0.23	0.19	0.16
≥1 year interval	264	0.17	0.30	0.24
Contralateral breast and <1 year interval	416	0.47	0.63	0.54
Contralateral breast and ≥1 year interval	237	0.20	0.40	0.32
<i>In situ</i> /invasive				
Include all	465	0.01	0.18	0.08
Contralateral breast	153	0.21	0.21	0.17
<1 year interval	359	0.06	0.28	0.14
≥1 year interval	106	0.15	0.25	0.22
Contralateral breast and <1 year interval	93	0.33	0.27	0.21
Contralateral breast and ≥1 year interval	60	0.02	0.13	0.12

The main finding of the present study is that the morphological types of breast cancer are not genetically determined. The kappa values were close to 0 for morphology-specific familial breast cancers, analyzed in mother–daughter or sister–sister pairs. Such analyses are most convincing because the presentation of morphology is completely independent. Even the morphological presentation of first and second breast cancers, and *in situ* and invasive breast cancers were almost completely

random when restricted to contralateral cancers diagnosed more than 1 year apart. Such conditions are likely to define two independent primary tumours. The only exception was when ductal and lobular cancers were tested separately, for which the kappa value was 0.40.

The only observations that suggest a nonrandom presentation were confined to contralateral invasive tumours, diagnosed less than 1 year apart. The kappa value was

0.47 when all tumour types were tested and 0.63 when testing was confined to ductal and lobular types. These high kappa values were accounted for by lobular tumours. Lobular *in situ* or invasive breast cancer is often multifocal or bilateral at presentation, and even if unilateral this morphology has a tendency to predispose to cancer in the contralateral breast [3,13]. The high kappa values for tumours diagnosed less than 1 year apart suggest that the second cancer is not independent from the first one, and that it may be a recurring tumour. It may seem paradoxical that an increased kappa was found only for contralateral tumours diagnosed less than 1 year apart. The probable explanation lies in the instructions in the Swedish Cancer Registry regarding the reporting of multiple primary tumours. Tumours that are diagnosed temporally close together are likely to be reported as independent primaries if they occur contralaterally rather than ipsilaterally. Because practically all tumours reported to the Swedish Cancer Registry are histologically or cytologically verified, the reliability of the data is high, and this also applies to second primaries [14].

In summary, within the limits of the present sample size, the results suggest that morphological types of breast cancer are not genetically determined.

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